DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 19 1999

Mr. Randy J. Dennin
Capsugel Division
Warner-Lambert Company
535 N. Emerald Road
Greenwood, South Carolina 29646

Re: Docket No. 99P-1266

Dear Mr. Dennin:

This letter responds to your citizen petition dated May 3, 1999, requesting that the Food and Drug Administration (FDA) amend its regulation in Title 21 of the Code of Federal Regulations (21 CFR 101.36(f)(1)) to require that all dietary ingredients in dietary supplements be present at not less than 90 percent of the label declaration.

Your petition asks that FDA publish a proposed rule in the Federal Register to amend § 101.36(f)(1) to state:

> Products will be deemed to be in compliance with this section if the dietary ingredient content is at least equal to 90 percent of the value for that dietary ingredient declared on the label. The product will also be deemed to be in compliance if it is [sic] conforms with the specifications of an official compendium. Reasonable excesses of dietary ingredients over labeled amounts are acceptable within current good manufacturing practices.

In accordance with 21 CFR 10.30(e)(3), this letter is to advise you that FDA is denying your petition, without prejudice.

In your petition, you state that FDA should amend its regulation to provide a less stringent compliance requirement for Class I nutrients incorporated into dietary supplements because:

1. The current regulatory requirement for measuring potency was developed for conventional foods and therefore is not appropriate for dietary supplements and, furthermore, the current requirement does not recognize the fact that the definition for dietary supplement in 21 U.S.C. 321(ff) makes clear that dietary supplements should be treated differently from conventional foods;

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2. The current regulatory requirement erroneously assumes that all dietary supplements are fabricated, fortified products and the current requirement in § 101.36(f)(1) does not recognize that not all dietary supplements are fabricated or fortified products;

3. Most dietary supplement ingredients degrade naturally over time and imposing a 100 percent potency requirement will require manufacturers to formulate their products with substantial overages that will increase manufacturing costs, which will then be passed on to consumers;

4. FDA should allow a lower limit of 90 percent potency because this is consistent with the statutory requirement that permits dietary supplements to conform to compendial standards; and

5. Dietary supplements are more appropriately regulated for potency using standards established for ensuring potency of drug products because dietary supplements are formulated with dietary ingredients that, like drugs, have an impact on the structure and function of the body.

Class I nutrients are those nutrients that are added to fortified or fabricated foods in controlled amounts. The 100 percent rule in 21 CFR 101.9(g)(4)(I) specifies that a food is considered misbranded if a Class I nutrient is present in an amount less than 100 percent of the amount declared on the nutrition label. The regulation also specifies that a food is considered misbranded if a Class II nutrient is present in an amount less than 80 percent of the amount declared on the nutrition label. Class II nutrients are those nutrients that are naturally occurring (indigenous) in the food and whose level is not controlled or manipulated by the manufacturer. This regulation also states that no regulatory action will be based on a determination of the amount of a nutrient value that is less than the 100 or 80 percent amounts by a factor less than the variability generally recognized for the analytical method used in that food at the level involved. Section 101.36(f)(1) states that "the criteria on class I and class II nutrients given in § 101.9(g)(3) and (g)(4) also are applicable to other dietary ingredients described in paragraph (b)(3)(I) of this section. Reasonable excesses of these other dietary ingredients over labeled amounts are acceptable within current good manufacturing practice."

A substance required to be declared on the label of a dietary supplement becomes part of a product in one of two ways: (1) it is a normal constituent of a source ingredient or another dietary ingredient that is included in the dietary supplement; or (2) it is intentionally introduced into the dietary supplement by the manufacturer in a given amount. In the latter case, because the level of the nutrient or substance in the source ingredient is determined or manipulated by the manufacturer, that substance is an "added" substance and subject to the 100 percent standard. This would be the case whether the added dietary ingredient is a substance that is isolated and purified from a natural source (for example, vitamin E isolated from a vegetable oil) or is synthetically prepared (vitamin E as dl-alpha-tocopherol acetate). A substance would also be added if the manufacturer manipulates its level in the source ingredient. For example, in a standardized herbal extract, because the manufacturer controls the amount of the standardized substance in the extract, that substance (the dietary ingredient) is an added dietary ingredient and is subject to the 100 percent standard.

In the former case, the dietary ingredient will be subject to the 80 percent standard because the manufacturer, even when required to disclose the amount of the substance, does not control the amount of the substance in the source ingredient. For example, the vitamin C in rose hips is a normal constituent of a source or dietary ingredient and its quantitative amount must be disclosed on the label of a dietary supplement under §101.36(b)(2). In this case, although the manufacturer controls the amount of rose hips added to the finished product to achieve a target amount of the nutrient desired, it does not control the natural variation in the vitamin C content of the rose hips. A similar situation would exist for many constituents of botanicals that a manufacturer might wish to make a claim about, such as the level of a particular ginsenoside in ginseng. In these two instances, because the amount of the individual nutrient or substance is controlled by the manufacturer only by the amount of the source ingredient used, the substance would be subject to the 80 percent standard.

FDA discussed the basis for requiring that an added dietary ingredient be present in a dietary supplement at 100 percent of the amount declared on the label in the preamble to the final dietary supplement labeling regulations published in the September 23, 1997 Federal Register (62 FR 49826 at 49838). Your petition provides no basis for FDA adopting a compliance policy regarding the amounts of added substances in dietary supplements that is different from the policy required by the current regulations.

You state, first, that the regulatory requirement that applies to the amount of a dietary ingredient added to a dietary supplement should not apply to dietary supplements because the requirement was developed for conventional foods and not dietary supplements. You also state that the current requirement does not recognize the fact that the definition for dietary supplement in 21 U.S.C. 321(ff) makes clear that dietary supplements should be treated differently from conventional foods.

FDA rejects the argument that the statute requires that dietary supplements should be treated, for compliance purposes regarding the amounts of added substances, differently from conventional foods and that because FDA first developed the current compliance requirements for added nutrients for conventional foods, those requirements are inappropriate for application to dietary supplements. The Federal Food, Drug, and Cosmetic Act (the act), as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), states: "Except for purposes of paragraph (g) [of 21 U.S.C. 321], a dietary supplement shall be deemed to be a food within the meaning of th[e] [act]." 21 U.S.C. 321(ff). Therefore, the language of the act clearly states that dietary supplements are foods. By logical extension, the agency may treat them the same as foods for this purpose. FDA finds nothing in the language of DSHEA, or in the statement of agreement that accompanied it and that comprises the sole legislative history of DSHEA, that supports FDA adopting a compliance policy regarding the amounts of added substances in dietary supplements that is different than the policy for foods. FDA finds no compelling reasons, therefore, that would support treating these two product types in a different manner for these compliance purposes.

You assert that FDA erroneously assumes that all dietary supplements are fabricated, fortified products and that current § 101.36(f)(1) does not recognize this fact. FDA disagrees. As discussed previously, current § 101.36(f)(1) clearly requires that only dietary ingredients that

are intentionally added to a product by, or whose level in a product is manipulated by, a manufacturer must be present at 100 percent of the declared amount. Dietary ingredients that are present in a dietary supplement by virtue of being a component of a naturally occurring source ingredient only must meet the 80 percent compliance standard for Class II nutrients. Therefore, the regulation explicitly recognizes the fact that dietary supplements can contain dietary ingredients that are subject to the 80 percent compliance standard and not the 100 percent standard.

You state that because dietary supplements degrade naturally over time, requiring that the ingredient be present at 100 percent would necessitate that manufacturers formulate their products with substantial overages that will result in higher costs for consumers. FDA finds no merit in this argument for requiring a different compliance standard regarding the amounts of added dietary ingredients. A guiding principle articulated by Congress in the findings accompanying DSHEA is that consumers should have access to dietary supplements as a means to supplement their diet in order to maintain and promote good health. For consumers to be able to make informed purchasing decisions and to have confidence in statements made on the label about the quality or benefits to the use of a dietary supplement product, the information on the label must be accurate and reliable.

Consumers may base their decisions to buy a product on, among other things, the amount of a substance they want in a product - based on information they have on the purported benefits of a substance - and cost. If consumers are not willing to pay for a product with a certain amount of the desired dietary ingredient, then they can select an alternative product with a lower amount of the dietary ingredient in it that they are willing to pay for. At the same time, if they spend their money to purchase a product with a certain level of a substance, they should receive a product that, in fact, contains that level of the substance. Your proposed compliance standard regarding the amounts of added substances would preclude consumers from making product choices based on the declared amount of a substance present. The current regulatory requirement of 100 percent ensures that consumers get what they are willing to pay for. We do not find any compelling support in your petition for FDA to conclude that a lower compliance standard for amounts of added substances would further consumers' ability to select products that they judge to be appropriate for themselves.

A manufacturer, to declare on a product label that a constituent is present at a certain level, must have a basis to conclude that the declaration is valid throughout the shelf life of the product. That basis necessarily includes: (1) an understanding of the stability of the substance in the product; and (2) knowledge of the amount of the substance in the product based on a scientifically valid method. The degree of confidence that a manufacturer has in a label declaration of an added substance, be it a vitamin, mineral, botanical constituent or other dietary ingredient, in part reflects its confidence in the accuracy and precision of the analytical method used. The confidence that a manufacturer has in its ability to formulate a product that contains what it purports to contain throughout the shelf-life of its products will be the same whether a product must contain 90 percent or 100 percent of the declared amount. If it can not predict what it takes to ensure compliance at 100 percent, we do not see how it could predict what would be needed to ensure compliance at 90 percent. Additionally, if overages of a substance are necessary to ensure compliance over an extended shelf-life with the 100

percent standard, similar overages would be necessary to ensure compliance with a 90 percent compliance standard. Lowering the compliance standard for amounts of added substances would only afford manufacturers, at the expense of consumers purchasing the products, a mechanism to market products that do not meet the label declarations for added dietary ingredients. If a manufacturer can not validate compositional claims made for a product within the limits of variability of the analytical method used and over the shelf-life of the product, it should not make such claims for a given product.

You state that FDA should allow a lower limit of 90 percent potency for added substances because this limit is consistent with the statutory requirement that permits dietary supplements to conform to compendial standards. FDA agrees that 21 U.S.C. 343(s)(2)(D) provides that a dietary supplement may be represented as conforming to the specifications of an official compendium. 21 U.S.C. 343(s)(2)(D) does not require that FDA adopt a particular compendial standard. In fact, for products that may be marketed as dietary supplements in the United States, different compendia exist that have widely differing approaches to compliance standards[1]. The petition provides no compelling reason why its proposed standard of 90 percent is superior to other compendial standards that are available, or to the agency's current standard. The agency remains convinced that consumers are best served by a standard that ensures that products contain what they purport to contain while they are available in the marketplace.

FDA also rejects the argument you put forward that FDA is obligated to adopt the United States Pharmacopeia (USP) 90 percent standard because the National Technology Transfer and Advancement Act of 1995 (NTTSA Act) and OMB Circular A-119 direct agencies to use voluntary consensus standards. Contrary to the assertion in the petition, OMB Circular A-119, which implements the NTTSA Act, specifically states that standards of the USP are not voluntary consensus standards under the NTTSA. OMB Circular A-119; Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities, 63 FR 8546, 8554 (Feb. 19, 1998).

Finally, you state that because FDA uses a potency range as its compliance standard for the amount of an active ingredient in drug products, it is inconsistent for the agency to apply a different compliance standard for the amounts of substances in dietary supplements. You state that dietary supplements are analogous to drugs because both product types contain active ingredients, are intended to affect the structure or function of the body, and are manufactured using similar technological processes. You assert that, because of these similarities, dietary supplements should be held to the same compliance requirement as are drugs (i.e., use of potency ranges (as is the case for drugs) rather than a 100 percent rule (as is now the case for dietary supplements)). FDA finds no merit in the argument that the compliance standard for amounts of added substances in dietary supplements should be determined by what the compliance standard is for a different category of FDA regulated products, such as drugs. Many conventional foods contain added nutrients or other added

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[1] For example, the German Pharmacopoeia (Deutsches Arzneibuch) has compositional requirements that range from requiring plus or minus a certain percentage of a substance to standards of "not less than" a given amount.

substances that could be considered to be "active" ingredients, are intended to affect a structure or function of the body (see 21 U.S.C. 321(g)(1)(C)), and are manufactured in a similar manner to dietary supplements. Therefore, your argument, rather than compelling the conclusion you propose, also justifies a conclusion that these two types of food products should be subject to the same compliance standards for amounts of added substances, which is consistent with FDA's current regulations.

As we have said above, consumers elect to use dietary supplements to supplement their dietary intake of specific substances to promote good health. Drugs contain a dosage or range of dosages that FDA has determined, before they are marketed, are safe and effective for an intended use or uses based on extensive data that a sponsor has provided to FDA. Because FDA approves drug products, consumers and health care providers are assured that a product that meets the appropriate standards will be safe and effective for its intended use. However, dietary supplements are not generally subject to premarket scrutiny or approval by FDA. Manufacturers of dietary supplements are not required to submit evidence to show that a particular formulation will produce a specific claimed outcome. If a product is represented to have a specific effect on structure or function or is promoted for a specific benefit when a particular amount is consumed, then consumers will make purchase and use decisions, in part, on that information. Those decisions will not be informed decisions, nor will consumers have any assurance that a product will produce the desired outcomes, unless they can be assured that the product contains what it is labeled to contain. Absent a premarket approval process that establishes a dosage range in which a consumer can be assured that a dietary supplement's claimed benefits occur, FDA is convinced that consumers are best served by a requirement that a dietary supplement product to which a dietary ingredient is intentionally added be required to have the quantity of that added substance that is declared on the label.

For the reasons discussed above, FDA is denying your petition without prejudice.

Sincerely,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs

cc:
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